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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/588,314	06/06/2000	Brian S. Hooker	059440/0128	9635

7590 08/14/2002

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EXAMINER
SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/14/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/588,314	HOOKER ET AL.	
	Examiner	Art Unit	
	Mary Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-15 and 18-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,13-15 and 18-23* is/are rejected.

7)☒ Claim(s) *12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 June 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Objections

1. The claims are objected to since the species name "agrobacterium" is not capitalized and italicized, "*Agrobacterium*". Correction is required.

2. Claim 12 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 12 specifies that the human coagulation factor VIII is a full-length sequence. This limitation overcomes the 35 U.S.C. 112, scope of enablement rejection and the 35 U.S.C. 103 (a) rejection in view of the 37 CFR 1.132 declaration submitted 4/2/02 by Dr. Brian S. Hooker showing unexpected results for expression of the full-length human coagulation factor VIII over the prior art cited in the previous Official Action.

Claim Rejections - 35 USC § 112

3.The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23, part (a) was amended to recite " modifying a coagulation factor VIII a sequence encoding human coagulation factor VIII for subcloning into a plant expression vector". This phase is indefinite since it is grammatically incorrect. It appears that the first "a coagulation factor VIII" phrase after "modifying" and before "encoding" should have been deleted so that the phase read "modifying a sequence encoding human coagulation factor VIII for subcloning into a plant expression vector."

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-10, 13-15 and 18-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 was amended to claim methods of producing bioactive human coagulation factor VIII via subcloning a sequence encoding a human coagulation factor VIII into a plant expression vector. The claim does not specify that the human coagulation factor VIII is a full-length gene. Similarly, claims 6, 15 and 23 were amended to recite that the coagulation factor VIII is human, but do not specify that the coagulation factor is full-length.

Claim 13 as amended specifies that the encoding sequence encodes a full length human coagulation factor VIII deleting a B-domain. Claim 23 as amended claims modifications of the coagulation factor VIII.

The claims thus read on administration of any size (any length) and modification of the human coagulation factor VIII for expression in plants.

The specification as filed and the 37 CFR 1.132 declaration by Dr. Brian Hooker teach successful administration of the full-length human coagulation factor VIII to tobacco plants. Applicant writes on page 7 of the response filed 4/2/02 that expressing such a large protein in plants is a "significant achievement and contribution to this important scientific field in providing the first successful production of large and complex protein, a human coagulation factor VIII, in a transgenic plant. In fact, a human coagulation factor VIII is by far the largest single frame protein ever expressed in a transgenic plant."

However, the claims as written continue to read on a breath of species of any length (since the length is not specified, and some of the claims specify deletions) and any modification of human coagulation factor VIII not adequately described in the specification as filed. Neither the specification nor the prior art taught a representative number of species of any fragment, deletion or modification of human coagulation factor VIII transformed into plants.

MPEP 2163 teaches the following conditions for the analysis of the claimed invention at the time the invention was made in view of the teachings of the specification and level of skill in the art at the time the invention was made:

The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence....A lack of written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process....Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement....The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

In the instant case, the claims are claiming expression of any "bioactive" human coagulation factor VIII in plants, but applicant has only shown the expression of full-length human coagulation factor VIII (in the declaration filed 4/2/02). From the teachings of the specification as filed and the declaration, one skilled in the art would not have recognized that applicant was in possession of a representative number of species of other protein lengths, amino acid compositions, and modifications of human coagulation factor VIII expressed in the plant having a "bioactive" function as claimed. Neither the specification nor the declaration taught the significant sequence structures of the full-length human coagulation factor VIII which would have produced in plants the "bioactive" protein claimed. Thus there were no identifying characteristics (ie. specific sequence structure) correlating to known biological function taught in the specification, so that one of skill in the art could readily envisage the pertinent portions of the

protein that were necessary for the claimed "bioactive" function of the protein upon expression in plants. Without this teaching, one of skill in the art would not have known what fragments or modified versions of the disclosed human coagulation factor VIII would have been suitable for expression in plants of a bioactive protein (having the correct secondary and tertiary structure necessary for protein function) at the time the invention was made. Without an adequate description of the significant structural features necessary, the specification as filed has not provided an adequate description of a representative number of species of any such modification or portion of the full-length human coagulation factor VIII.

The claims are adequately described for expression of a "full-length human coagulation factor VIII" and for claims where analogous porcine sequences are used in the full-length human coagulation factor VIII (since the prior art taught use of porcine sequence substitutions).

7. Claims 1-10, 13-15 and 18-23 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of expression of a full-length human or porcine/human chimera coagulation factor VIII having a "bioactive" function in plants, does not reasonably provide enablement for methods of expression of any encoding sequence having any fragment and/or modification of human or chimera coagulation factor VIII as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant states on page 7 that "the examiner clearly fails to appreciate applicants' significant achievement and contribution to this important scientific field in providing the first successful production of large and complex protein, a human coagulation factor VIII, in a transgenic plant." In view of the declaration provided by applicant, this contribution is not understood and the merits of this achievement are reflected in the instant Official Action. The claims have been found free of the prior art and enabled for the administration of full-length human or porcine/human chimera coagulation factor VIII for expression in any plant (the limit to tobacco is withdrawn).

However, the claims continue to embrace any non-full-length human coagulation factor VIII, which includes fragments and modifications thereof for administration to plants. This breath of sequences is not enabled for expression in plants of a protein having a "bioactive" function since neither the specification nor the prior art taught which fragments and/or modifications of the full-length human coagulation factor VIII will allow for a bioactive function specifically in plants. Brenner, Smith et al., Skolnick et al., Bork, Ngo et al., and Wells were cited in the previous Official Action to teach in general the difficulties in determining protein function from sequence structure alone. Although human coagulation factor VIII was characterized in the prior art (as seen in the references cited in the previous Official Action: Hoeben et al., Healey et al., Lollar et al., Stein et al. and Lubin et al.) for use in mammals, and thus some sequence structure/function correlation was known, such results to not necessarily correlate to the same results in plants. As per applicants own admission, expression of the full-length sequence was unexpected in plants prior to applicants invention. The fact that the full-

length human coagulation factor protein was expressed as per applicants showing does not mean that any fragment or modification thereof will be able to be expressed to make a "bioactive" protein in plants. Making a bioactive protein depends on having the right amino acid sequence so that the secondary and tertiary considerations are met and the protein is able to fold into a bioactive state. One of skill in the art would need to practice "trial and error" experimentation to make and use any fragment or modification of the claimed human coagulation factor VIII since neither the specification nor the prior art taught the specific fragments and/or modifications that function to make bioactive human coagulation factor VIII when specifically expressed in plants as opposed to mammals.

Applicant notes that the "standard for determining enablement is whether the specification as filed provides sufficient information as to permit one skilled in the art to make and use the claimed invention....The test of enablement is not whether experimentation is necessary, but rather whether any experimentation that is necessary is undue.... Thus, neither the breadth of claims nor the absence of working examples is a dispositive factor. Similarly, enablement does not require actual reduction to practice. In addition, since only an enabling disclosure is required, applicant needs not describe all actual embodiments.... Moreover, it is "not a function of the claims to specifically exclude inoperative substances."... The question is not whether all embodiments are operative, but whether one of skill in the art could determine which ones are operative."

Since the claims cover embodiments of any length of human coagulation factor VIII, not just full-length, since there was not guidance in the prior art or the specification as to which

fragments of human coagulation factor VIII, upon expression in plants, would make a bioactive human coagulation factor VIII, since the prior art taught that it was not predictable whether the plant would be able to make a bioactive human protein having the same structure (modifications, 3D structure) as in human (see Cramer et al. Pages 63-67), and since the specification (the declaration) taught only expression of the full-length human coagulation factor VIII in plants, one of skill in the art would necessarily practice undue experimentation to make and use any such fragment or modification thereof.

Applicant argues on page 8 of the response, first full-paragraph, that the functional domains of human coagulation factor VIII were known in the prior art and that "it would not have required undue experimentation at the time of filing of the instant application to identify nucleotide sequences coding for human factor VIII protein, or functional fragments of human factor VIII protein, for expression in transgenic plants." However, Cramer et al. taught that while there has been good success of expression of human proteins in plants, this is still not a predictable event. They taught that in the case of complex proteins, such as human protein C, having a heavy chain and a light chain, substantial proteolytic processing is involved to make the final protein. Although Cramer et al. taught that human protein C was able to undergo similar post-translational processing in tobacco plants as in humans, such results must be determined on a protein-by-protein basis. In the case of human coagulation factor VIII, Lollar et al. taught that "human and porcine factor VIII (fVIII) are activated by thrombin to form a heterotrimer composed of subunits designated A1 and A2 derived from the fVIII heavy chain (HC) and a subunit designated A3-C1-C2 derived from the fVIII light chain (LC)." As per applicants

assertion, full-length human coagulation factor VIII is the largest protein to ever be expressed transgenically in a plant. However, such results do not correlate to the expression of any fragment thereof for expression of a bioactive protein. The references cited by Applicant do not teach expression of fragments of human coagulation factor VIII in plants. Without such guidance as to which fragments would be able to be expressed in plants, one of skill in the art would necessarily practice trial and error experimentation to make bioactive fragments in plants.

In regards to making modifications of human factor VIII for expression in plants, Applicant points to the instant specification that cites Ausubel et al. as teaching standard molecular cloning procedures for modifying encoding sequences such as adding a transcription promoter and transcription terminator. However, the term "modify" when given its broadest reasonable meaning, includes many other possible sequence modifications than adding transcription promoters and terminators, the breath of which is not enabled by the teachings of the instant specification for making a "bioactive" human coagulation factor VIII. Although the addition of a promoter and terminator is enabled (such as specified in instant claim 19), the addition of foreign sequences into the coding region of the human coagulation factor VIII for instance would not be enabled for making a bioactive human coagulation factor VIII for instance. Thus, when the claims are given their broadest possible interpretation as per MPEP 2111.01 for examination purposes, the claims are not enabled for any modification of the full-length human coagulation factor VIII as presently claimed.

In view of the unpredictability in the art for expression of any length and any modification of full-length human coagulation factor VIII as broadly claimed, and in view of the

lack of guidance in either the specification or the prior art for determination of the specific regions of human coagulation factor VIII, that when expressed in plants will enable expression of a bioactive protein, one of skill in the art would necessarily practice trial and error experimentation to make and use the invention as claimed.

8. The closest prior art to the claimed invention was cited in the previous Official Action mailed 10/02/01 as Cramer et al. in view of Hoeben et al., Healey et al., Lollar et al., Stein et al. and Lubin et al. which was relied upon to teach the expression of non-plant, such as human, proteins in tobacco plants (Cramer et al.) and the expression of human coagulation factor VIII and its use in mammals (Hoeben et al., Healey et al., Lollar et al., Stein et al. and Lubin et al.). The rejection was withdrawn in view of applicants declaration showing unexpected results for expression of full-length human coagulation factor VIII in plants because of its substantial size.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Kay Pinkney*, whose telephone number is (703) 305-3553.

M. M. Schmidt
August 11, 2002